Table 1. Association between *TM6SF2* rs58542926 variant and NAFLD.

Genotype count			
Genotype	CC	CT	TT
Control	333	33	0
Case	302	65	0

Statistical analysis*					
Unconditioned		Condition on rs738409		Condition on rs2228603	
OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
2.2 (1.4-3.4)	0.0007	2.3 (1.4-3.6)	0.0004	2.1 (1.4-3.4)	0.001

*Associations were tested using logistic regression with adjustment for age, sex, BMI and status of diabetes.

OR, odds ratio; CI, confidence interval.

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Is it worthy of switching to PegIFN alfa-2a in patients achieving virological suppression with entecavir?

To the Editor:

We read with great interest the article "Switching from entecavir to PegIFN alfa-2a in patients with HBeAg positive chronic hepatitis B: A randomized open-label trial (OSST trial)" [1]. This elegant study assessed the rates of HBeAg seroconversion and HBsAg loss in patients with well-controlled HBV DNA replication and serum HBeAg <100 PEIU/ml on long-term entecavir (ETV) therapy after switching to a finite course of PegIFN alfa-2a. Qin Ning *et al.* [1] demonstrated that switching to a finite course of PegIFN alfa-2a significantly increased rates of HBeAg seroconversion and HBsAg loss and concluded this is a potential alternative to indefinite nucleos(t)ide analogue (NA) therapy.

Many chronic hepatitis B patients are treated with ETV in China. Some of them hope to stop this infinite treatment if a finite course of treatment can give similar or better outcomes with a reasonable cost and minimal adverse effects. In Shenzhen, patients receiving sequential therapy with NA and PegIFN are not rare. However, there are several concerns about this article and its approach. First, the absolute difference in HBeAg seroconversion rate was only 8.8%. In other words, the number to treat for one HBeAg seroconversion is 11. All these patients have to suffer the adverse effects of PegIFN. It is well known that hepatic decompensation and even death has been reported during IFN treatment. We should also pay special attention to the adverse effect of stopping of ETV. Hepatic decompensation or liver failure was not recorded in the study given the sample size. Recently, one of my patients developed acute on chronic liver failure during PegIFN treatment after stopping ETV and adefovir (ADV) which was reported on in a local hepatology meeting. The effect of an overlapping period of ETV and PegIFN on safety and efficacy

remains unclear. Second, the other endpoints of HBV DNA suppression <1000 copies/ml and ALT normalization after 48 weeks of PegIFN treatment was unsatisfactory. These results might be worse after withdrawal of PegIFN therapy. Most of the patients had to resume ETV treatment, which is terrible news for a doctor to have to deliver to patients after a long course of PegIFN therapy. Third, sustained and profound viral suppression is the main goal of treatment. The fluctuation of ALT and HBV DNA in the sequential therapy may mimic the phenomena of viral resistance to NA. It has been reported that treatment related viral resistance blunts histologic responses [2] and increases the rate of hepatocellular carcinoma (HCC) even if rescue therapy is given [3]. Fourth, the cost of treatment should also be considered. The per capita disposable income is 18,311 RMB (≈2982 USD) in China 2013. The cost of 48 weeks of PegIFN treatment is about 50,000 RMB (≈8143 USD). Most of the treatment-naïve patients in China may find this treatment unaffordable. The cost of 48 weeks ETV is only one fifth of that. Fifth, the causative agent has not been identified in this randomized controlled study. The treatment arm underwent ETV withdrawal and PegIFN. Withdrawal of ADV after 4–5 years of therapy has been shown to result in 39% HBsAg loss in selected HBeAg negative patients [4]. To date, there has never been a parallel study in HBeAg positive patients, and there has never been a randomized control trial with PegIFN that involves a control arm with NA withdrawal only. We are anxiously waiting for such a study, we can no longer make the assumption that the treatment effect is entirely due to PegIFN. The correlation between early ALT elevation after withdrawal of ETV with HBeAg seroconversion and HBsAg loss supports this hypothesis. Finally, the benefit of HBeAg seroconversion should not be over emphasized. HBeAg seroconversion has long been regarded as an important treatment endpoint in hepatitis B therapy. However, with the prevalence of pre-core or core mutation HBV infection, HBeAg seroconversion is no longer an ideal endpoint. Recently, Jessica Liu *et al.* demonstrated that HBV DNA seroclearance, during the course of chronic hepatitis B, is the most significant factor in reducing risk for future HCC and HBeAg seroclearance will not reduce future HCC further [5]. Combination endpoint with HBeAg seroconversion and HBV DNA <1000 copies/ml may be more reasonable as the primary endpoint. We do not know if the significant difference between the two cohorts was lost with this endpoint.

In summary, as clinicians, after weighing the pros and cons, we do not think it is worthy of switching to PegIFN in patients achieving virological suppression with ETV, except if the patient refuse a long-term treatment.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Repeated transarterial chemoembolization: An overfitting effort?

To the Editor:
We read with great interest the article by Adhoute *et al.* published in *Journal of Hepatology* [1]. The authors developed a point score system, the ABCR [standing for Alpha-fetoprotein (AFP), Barcelona Clinic Liver Cancer (BCLC), Child-Pugh and Response], to assist in the decision making on whether to retreat hepatocellular carcinoma (HCC) patients with multiple transarterial chemoembolization (TACE) sessions. The study population consisted of HCC patients treated with repeated consecutive TACE sessions and the resulting significant parameters from regression analysis were used to build the score. In this way, the authors differentiated three groups with different survival. The score was consistently validated in training and confirmatory cohorts and a higher ABCR score after the first TACE course was found to be associated with patients at poorer prognosis who may not benefit from further TACE sessions.

Current guidelines do not specify the criteria for repeating TACE and the correct number of repeated procedures to undertake, hence the paper by Adhoute *et al.* is certainly of interest.

However, it should be noted that patients in more advanced BCLC stage and with higher baseline AFP levels, namely those requiring further treatment repetitions are considered less likely